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Developing a paradigm of drug innovation: an evaluation algorithm

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Assessment of drug innovation is a burning issue because it involves so many different perspectives, mainly those of patients, decision- and policy-makers, regulatory authorities and pharmaceutical companies. Moreover, the innovative value of a new medicine is usually an intrinsic property of the compound, but it also depends on the specific context in which the medicine is introduced and the availability of other medicines for treating the same clinical condition. Thus, a model designed to assess drug innovation should be able to capture the intrinsic properties of a compound (which usually emerge during R&D) and/or modification of its innovative value with time. Here we describe the innovation assessment algorithm (IAA), a simulation model for assessing drug innovation. IAA provides a score of drug innovation by assessing information generated during both the pre-marketing and the post-marketing authorization phase.

The last decades of the twentieth century were marked by a continuous increase in life expectancy; at the same time, the development of new innovative drugs for care of patients has become fundamental to improve quality of life and to manage chronic diseases [1]. In the past few years, however, the number of new chemical entities (NCEs) for pharmaceutical use submitted to both the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) has progressively declined (full reports available at http://www.fda.gov/oc/initiatives/criticalpath/white-paper.html and http://www.emea.eu.int/pdfs/general/direct/emeaar/AnnualReport2005.pdf, respectively; access verified May 2006), while the cost of pharmaceutical research and development has progressively increased [2–5]. The many strategies to manage the increasing cost of research and development have been discussed extensively [5–8].

Given these circumstances, a scientific tool is needed to assess the innovation provided by a new pharmaceutical product, both for public and private decision-makers and for pharmaceutical companies. Such a tool might help to enhance research into new drugs and their introduction onto the market.

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The aim of this study was thus to develop an algorithm for assessing drug innovation with the following requisites:

- to take into account and incorporate different properties of drug innovation;
- to provide a numeric weight (or points) as a measure of the innovative value of a drug;
- to re-assess innovation over time, by incorporating clinical evidence that has emerged after marketing authorization.

In this way, the innovative value of a drug is based on the assessments of clinical efficacy studies (in the pre-marketing phase), clinical effectiveness studies (almost always in the post-marketing authorization phase) and the onset of adverse drug reactions (ADRs) in the general population.

Although the resulting model, called the innovation assessment algorithm (IAA), should be considered as a tool that is specifically useful for regulatory purposes, it runs with information that is known during the early stage of R&D. Furthermore, with respect to the relationship between pharmaceutical companies and regulatory authorities, IAA might also be useful after introduction of a drug onto the market when new notable data on public health can emerge. Finally, pharmaceutical companies might select one product out of multiple in-licensing opportunities on the basis of the innovative value assessed by IAA.

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Proposed algorithm for evaluating drug innovation

At least three main factors influence, and probably determine, the innovative value of a drug: its potential to decrease mortality and/or morbidity and/or disability; its capacity to reduce the social cost of disease; and its contribution to enhanced social and economic progress. On the basis of the above general requisites, IAA has been developed and IAA software can be downloaded from the SIFEIT website (http://www.sifeit.it/IAA.html; see Appendix).

Figure 1 shows the decision tree-like structure of the algorithm. Starting from the root, the different branches or properties that contribute to the value of drug innovation are shown sequentially. Each decisional node (full square) leads to two or more alternative branches (e.g. Y_1 and Y_2, are two different features of the property Y). It is obvious that this structure requires choices between alternative branches. Each branch of the same property is associated with a progressively decreasing numeric weight. For example, there are two alternatives for a property expressing the therapeutic benefits of a drug: either it can cure a disease or control its progression, or it might have only an effect on symptoms. The former alternative is attributed a higher numeric weight than the latter.

Progressing through the algorithm from the root to the terminal branches (full triangles), the sum of the numeric weights or points associated with the branches selected gives the final score that represents the value of drug innovation. The tree-like structure of the algorithm is preset; nonetheless, the software allows modification of the numbers expressing numeric weights to meet the specific needs of the user (see Appendix).

The IAA comprises two parts: IAA-efficacy and IAA-effectiveness. The first part provides the IAA-efficacy final score, which is the sum of the numeric weights attributed to each selected branch, and incorporates valuable data coming out of clinical efficacy trials performed during the pre-marketing phase, whereas the second part provides the IAA-effectiveness final score, which is the sum of the numeric weight of each selected branch and incorporates the results of clinical effectiveness trials, generally performed after marketing authorization. The IAA-efficacy and the IAA-effectiveness final scores are then summed to obtain the IAA full final score, which expresses the value of drug innovation. Thus, the IAA full final score incorporates the results from efficacy studies, from effectiveness studies and from the reports of registered ADRs.

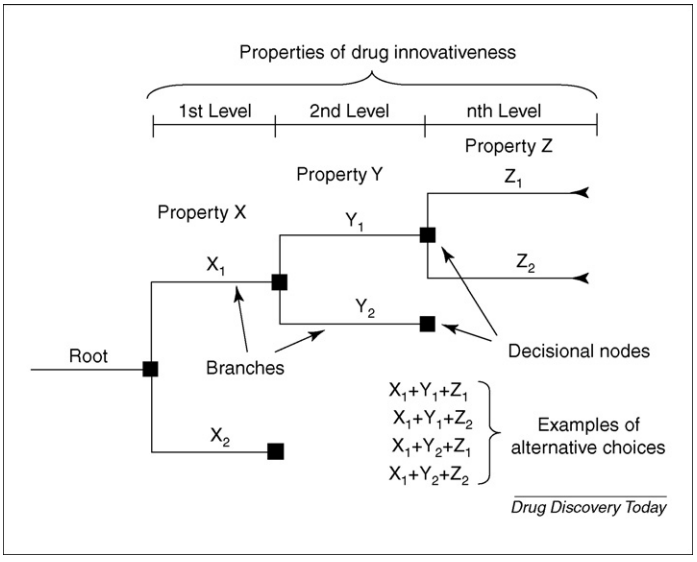

FIGURE 1

Tree-like basic structure of the innovation assessment algorithm (IAA). Starting from the root, the different branches or properties that contribute to the value of drug innovation are shown sequentially. Each decisional node (full square) leads to two or more alternative branches (e.g. Y_1 and Y_2, are two different features of the property Y). Progressing through the algorithm from the root to the terminal branches (full triangles) can result in various alternative outcomes, depending on branch selection.

The main difference between efficacy and effectiveness is related to the objective of the trial [9,10]: testing for efficacy involves demonstrating how a drug works under optimal conditions because the aim is to test the biological hypothesis; testing for effectiveness involves exploring the utility of a drug under usual practice conditions (i.e. to permit a choice between alternative treatments). In this way, different variables (selection criteria of the trial, the study size, and how the treatment comparison is made) might influence the outcomes of the efficacy estimation and the effectiveness evaluation of a new treatment in comparison to an older one.

On the basis of the principles stated in the declaration of the International Society of Drug Bulletins (ISDB) working group (available at http://66.71.191.169/isdbweb/pag/documents/ISDB-decl-english.pdf; access verified September 2006), the grid of the algorithm might be accessed from one of three roots. Each root leads to the expression of a different type of drug innovation: therapeutic innovation, common innovation or industrial innovation.

IAA-efficacy

The three roots of the IAA-efficacy tree develop into seven first-level branches (Figure 2), which are categorized as follows:

Therapeutic innovation root

- Branch A comprises NCEs (including those obtained through biotechnology) that have pharmacological action on a disease currently lacking treatment or with unsatisfactory therapeutic treatment.
- Branch B comprises NCEs (including those obtained through biotechnology) that are structurally not classifiable into any chemical class currently used in therapy (or previously described) and that have a new or known pharmacodynamic mechanism of action. For example, glitazones are hypoglycemic agents with a new mechanism of action (i.e. agonist action on peroxisome proliferator activating receptor type γ), whereas selective inhibitors of cyclo-oxygenase-2 are non-steroidal anti-inflammatory agents with a known, albeit more selective, mechanism of action on prostaglandin biosynthesis.
- Branch C comprises chemical entities that are known or structurally related to described compounds (with or without marketing authorization) and that have a new therapeutic indication (a new 'anatomic therapeutic chemical' classification). For example, α-1 adrenergic receptor blockers, such as terazosin, were formerly used only as anti-hypertensives, but they are now used to treat urinary disorders concomitant with prostate hypertrophy.

Common innovation root

- Branch D comprises NCEs that are structurally related to a chemical class that has been described for a similar therapeutic

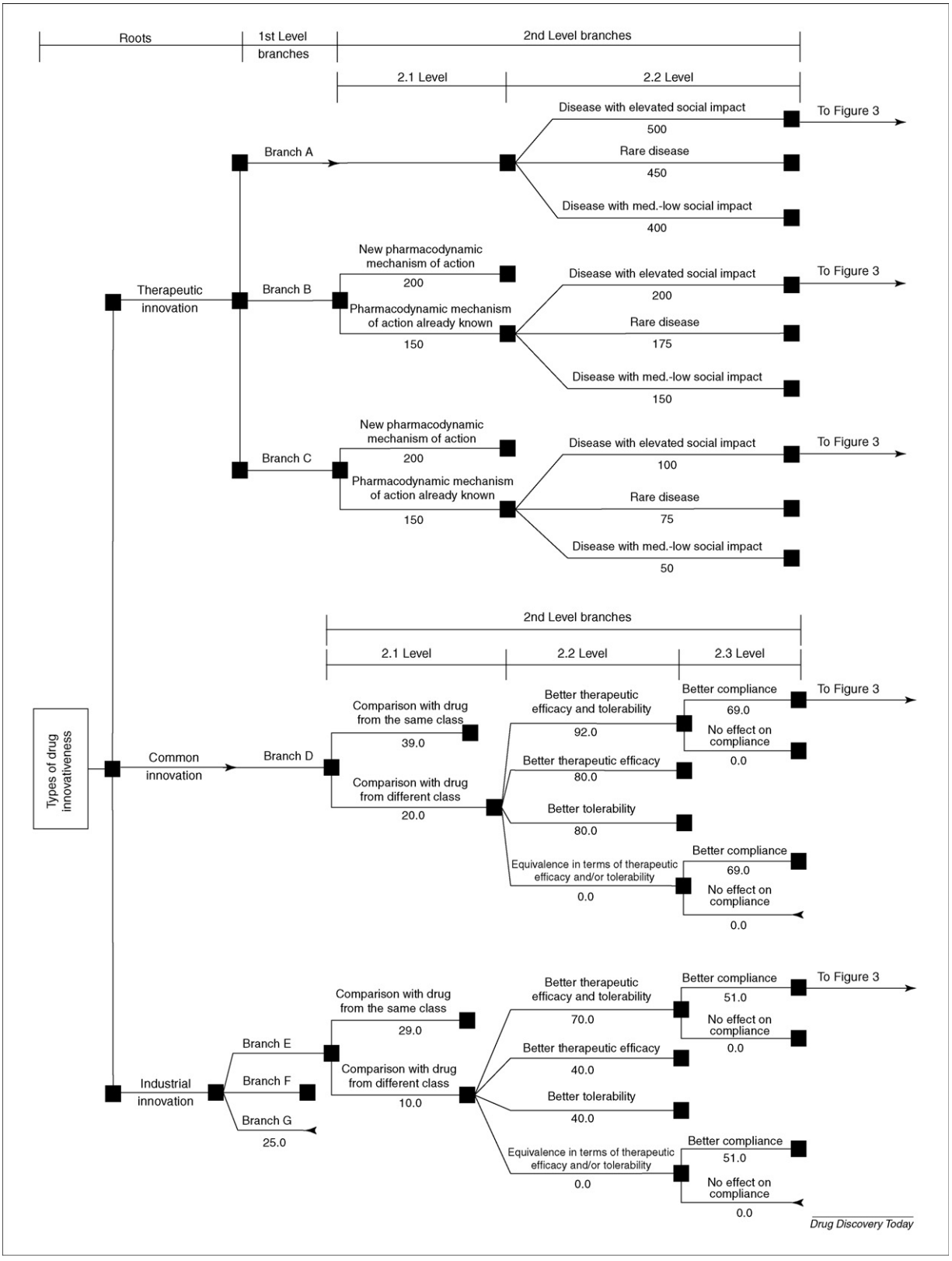

FIGURE 2

Access to the IAA: structure of IAA-efficacy showing first- and second-level branches. Numbers indicate the weights attributed to each branch.

indication (i.e. with an available anatomic therapeutic chemical code for at least the first three alphanumeric characters). This branch includes pro-drugs, derivates, conjugated drugs and associations.

Industrial innovation root

- Branch E comprises pharmaceutical products that are known and have been obtained through biotechnology or highly innovative technologies (recombinant DNA technology,

controlled expression of genes coding for biologically active proteins, hybridoma and monoclonal antibody methods).

- Branch F comprises known pharmaceutical products that have new characteristics of increased relevance regarding the pharmaceutical form and/or the administration mode.
- Branch G comprises known pharmaceutical products that have new characteristics of minor relevance regarding the pharmaceutical form or the administration mode and/or the improvement of the safety and/or handling of extemporaneous preparations. This is a terminal branch (full triangle).

Second-level properties of the IAA-efficacy tree

The second level of branches A, B and C in the therapeutic innovation root shows two properties (Figure 2): the drug's mechanism of action (new or known) and the social impact of the disease (levels 2.1 and 2.2, respectively). The criteria that contribute to defining the social impact of the disease stem from epidemiological and social impact data related to the geographic area of concern. To support the discovery and development of orphan drugs, the algorithm attributes a higher score to NCEs for rare diseases than to NCEs for diseases with medium or low social impact. The preset numeric weights of each branch are shown in Figure 2.

The second level of branch D in the common innovation root and of branches E and F in the industrial innovation root applies to NCEs, or to pharmaceutical products correlated to available drugs and directed at a similar therapeutic indication (Figure 2). The evaluation of drug innovation is based on the following criteria.

- Comparison with a drug from the same or different pharmacological class as that of the agent under study (level 2.1). A higher numeric weight is assigned to a comparison with a drug from the same pharmacological class. The alternative branch is a comparator chosen from active molecules from a different class.
- Assessment of efficacy and tolerability (level 2.2). Drugs in branches D, E and F are introduced into therapeutic fields in which valid alternatives already exist. Thus, these agents will have an innovative value only if they represent an advance in terms of efficacy, tolerability or compliance to treatment.
- Assessment of the patient's compliance to the treatment considered (level 2.3). A therapeutically equivalent drug (lower level of branch 2.2) can progress in the algorithm only if it is associated with a better compliance in comparison to other available drugs; otherwise, the drug should be considered void of innovative value.

It is worth highlighting the fact that the numeric weight of the different branches of IAA-efficacy decreases from branch A (high

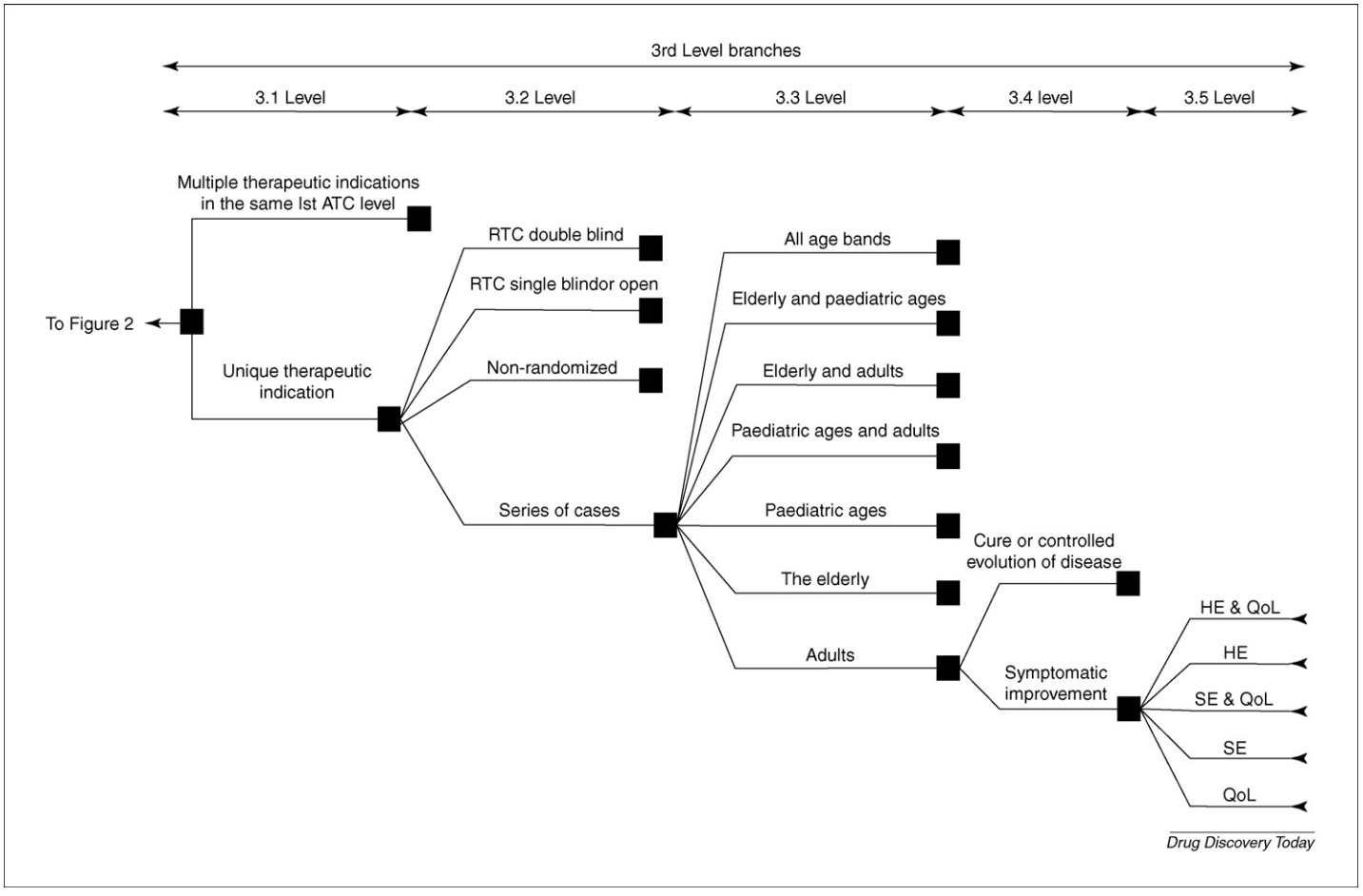

FIGURE 3

Final development of the structure of IAA-efficacy: third-level branches. Abbreviations: ATC, anatomical therapeutic chemical classification; RCT, randomized controlled trial; HE, hard endpoint; QoL, quality of life; SE, surrogate endpoint.

innovation, in that the drug is active in a disease for which there is no effective treatment) to branch G (pharmacological modifications of minor relevance to a commercially available drug).

Drugs obtained by biotechnological processes (e.g. proteins from recombinant DNA) are considered highly innovative only if they meet access criteria to branch A, B or C of the IAA-efficacy. Conversely, biotechnological drugs or drugs with novel pharmaceutical forms and/or administration modes that do not have any relevant therapeutic advantage for the patient cannot be considered highly innovative drugs, and therefore will access only branches E and F. For example, recombinant human insulin would access branch E, whereas interferon-β for the treatment of multiple sclerosis would access branch A.

Finally, a drug that accesses branch G might feature such characteristics that would enable its access to branches A to F described above. In this case, the IAA-efficacy final score for this drug would result from the weight obtained for branch G added to the weight obtained for the other branches.

Third-level properties of the IAA-efficacy tree

The IAA-efficacy has third level properties (Figure 3), which focus on the characteristics of the clinical studies conducted during the pre-registration phase. This level adds further weights to the IAA-efficacy final score on the following basis:

- number of therapeutic indications (level 3.1);
- design of clinical studies evaluating the clinical efficacy (level 3.2);
- age class of populations involved in clinical studies (level 3.3);
- type of drug benefit (level 3.4);
- type of clinical outcome (level 3.5).

IAA-efficacy score

Table 1 lists all of the numeric weights attributed to the different branches of the properties for each level of the IAA-efficacy. Overall, these weights were determined according to the following criteria:

- relevance of an alternative with respect to others in the same level (e.g. for the property 'design of clinical trial': the weight of a randomized, controlled clinical trial is higher than that of a series of cases);
- relevance of a single property in comparison to others (e.g. the weight of 'type of clinical outcome' is higher than that of 'age class of population involved in clinical trials');
- relevance of branch access (e.g. the weight of 'design of clinical trial' is greater in branch A than in branch D).

Furthermore, the numeric weights associated with 'design of clinical studies' and with 'type of clinical outcome' (levels 3.2 and 3.5, respectively) are subject to the individual judgment of the IAA-efficacy user in terms of the validity of the clinical outcomes and the robustness of the experimental design. The user can express three qualitative judgments: optimal, resulting in no reduction of the points that might be obtained for that specific property; sufficient, resulting in a 25% reduction of the points that might be obtained for that specific property, or poor, resulting in a 50% reduction of the points achievable for the specific property.

In quantitative terms, the principal contribution to the IAA-efficacy final score comes from the second-level properties insofar as they identify the main features (branches A, B and C) of drug innovation. For drugs with a slight innovative value (branches D, E and F), methodologically solid clinical trials (i.e. third-level

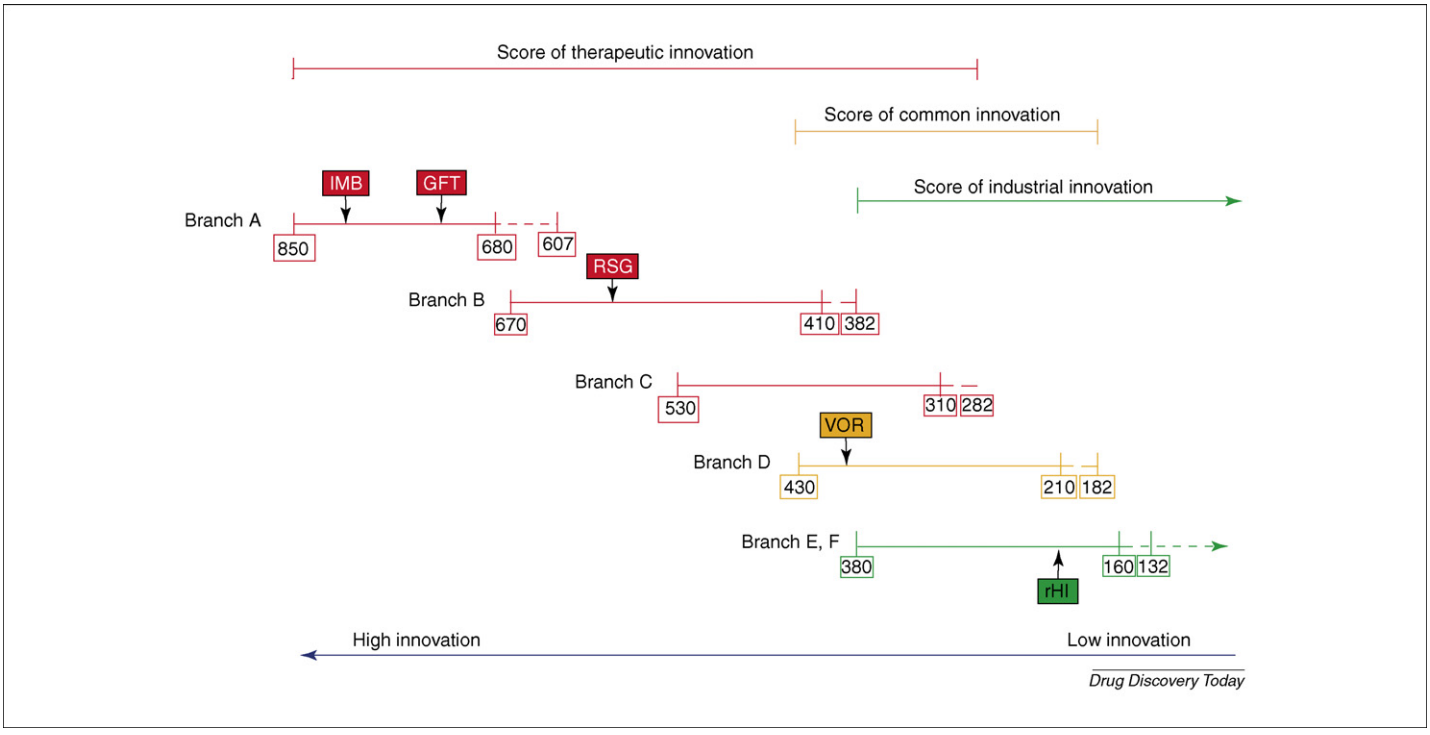

FIGURE 4

Score ranges according to the access branches of IAA-efficacy. Boxed numbers indicate the minimum and maximum scores. The range of score reduction owing to subjective assessment of both the quality of trial design and clinical endpoints is also indicated (broken lines). Also shown are examples of IAA-efficacy simulation for imatinib (IMB), gefitinib (GFT), rosiglitazone (RSG), voriconazole (VOR) and recombinant human insulin (rHI).

properties) might contribute to a higher final score of IAA-efficacy.

Figure 4 shows the maximum and minimum scores of IAA-efficacy, including reductions originating from the subjective judgment of the IAA-efficacy user on the quality of trials and outcomes evaluated. Examples of the use of the IAA-efficacy simulation on different drugs are also shown.

IAA-effectiveness

The second part of the algorithm is devoted to re-assessing the IAA-efficacy final score on the basis of the results of clinical effectiveness studies performed in the post-marketing phase. This re-assessment aims at incorporating the innovative value of a drug derived from its use in clinical practice and, thus, relative to real therapeutic benefits and ADRs observable in broad patients groups.

The access to this part of the algorithm basically depends on the availability of the results of the clinical effectiveness of a drug (Figure 5). The absence of data on drug effectiveness decreases the IAA-efficacy final score by 50%, except in the case of rare diseases or other specific situations, where the decrease depends on the severity or duration of the disease and according to the requirements of the user. Conversely, when drug effectiveness evidence is available, the IAA-effectiveness final score must be added to the IAA-efficacy final score.

Second- and third-level properties of the IAA-effectiveness tree

The IAA-effectiveness part of the algorithm was developed to evaluate the following second- and third-level properties.

- Size of clinical studies. The numeric weight attributed to evidence of clinical effectiveness is higher for data resulting from international studies than for those resulting from multicenter national ones. The points added by this property (level 2.1) are either 22.5 or 7.5 (Figure 5).
- Design of clinical studies or trials. This property should provide an overall qualitative assessment of the adequacy of the design of an effectiveness trial, which should consider both clinical and epidemiological characteristics of the disease for which the trial is being carried out. The points added by this property (level 2.2) range between 52.5 and 17.5.
- Appropriateness of comparator. This property is an overall qualitative assessment of the comparator's appropriateness; in other words, was the reference treatment sufficiently representative of therapeutic practice for the disease at the time when the clinical trial was started. The points added by this property (level 2.3) range between 52.5 and 17.5.

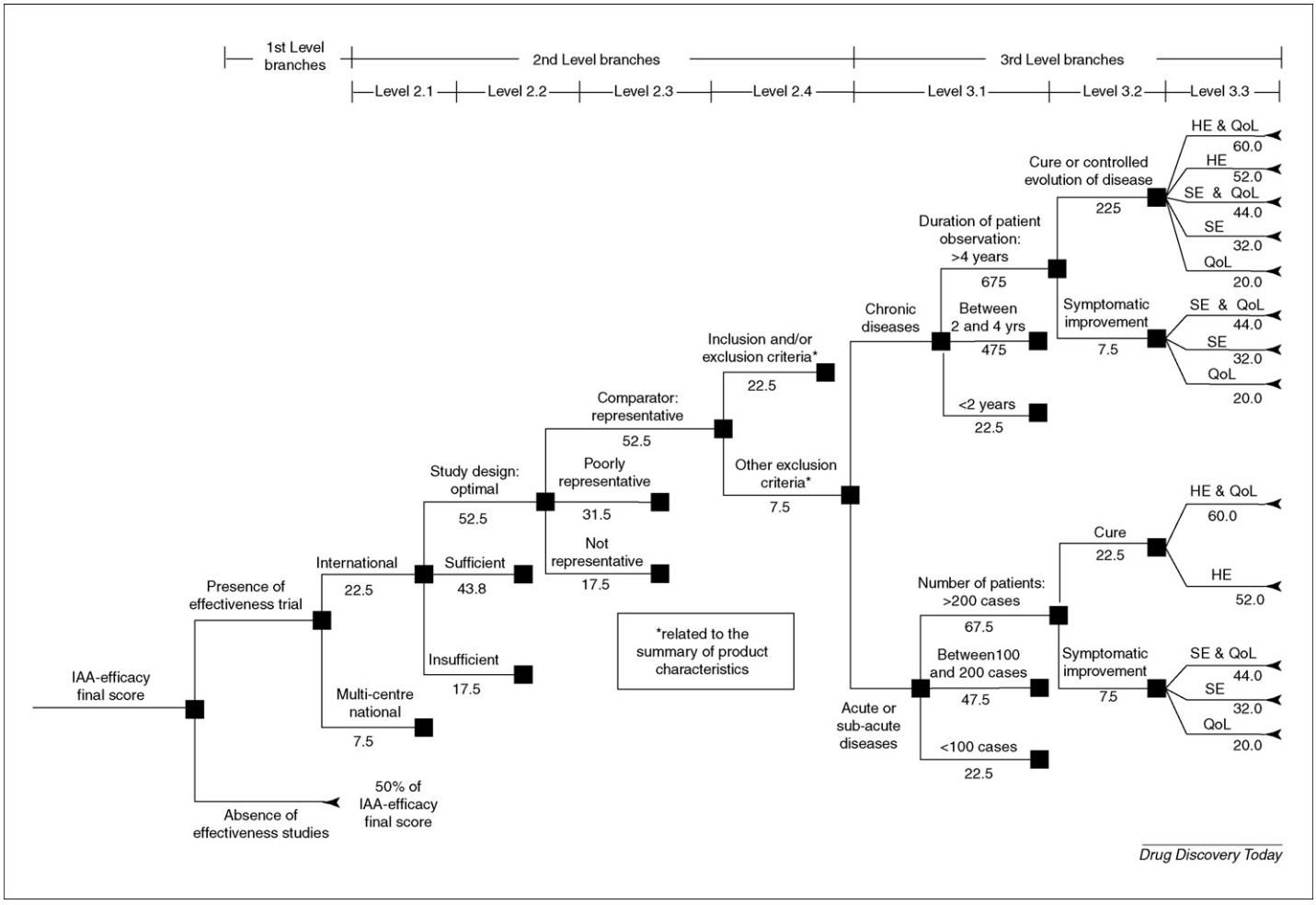

FIGURE 5

Final development of the structure of IAA: structure of IAA-effectiveness, showing first-, second- and third-level branches. Numbers indicate the weights attributed to each branch. Abbreviations: HE, hard endpoint; QoL, quality of life; SE, surrogate endpoint.

- Selection criteria of enrolled patients. Effectiveness trials need to enroll sample patients as similar as possible to those normally undergoing treatment in daily clinical practice. Thus, IAA-effectiveness attributes a higher weight to studies with inclusion criteria (based on the therapeutic indication) and exclusion criteria (based on the contraindications and precautions for use) provided from the pharmacological–toxicological characteristics of the product. The points added by this property (level 2.4) are either 22.5 or 7.5.
- Time span of observation and/or number of patients. The time span of a clinical study becomes relevant in chronic diseases: the longer the trial, the more relevant the evidence on drug effectiveness. Conversely, in acute or subacute illnesses, the sample size of the clinical trial becomes relevant: the larger the trial, the stronger the evidence on effectiveness. The points added by this property (level 3.1) range between 67.5 and 22.5.
- Type of clinical outcome and drug benefit. Regardless of the course of the disease, these properties are valued in a manner similar to that in IAA-efficacy (but they provide different additional weights). The points added by these properties (level 3.2 and 3.3) range between 60 and 7.5.

IAA-effectiveness score

The IAA-effectiveness final score can add a minimum of 100 to a maximum of 300 points to the IAA-efficacy final score. Furthermore, on the basis of safety data, assessed in the context of both studies conducted in clinical practice and ADRs reports recorded in phase IV of pharmacovigilance, the IAA full final score could remain unaffected in the absence of severe ADRs, or decreased in the presence of severe ADRs by between 50 (i.e. the best case of expected severe ADRs) and 200 points (i.e. the worst case of unexpected severe ADRs). Maximum point reduction, as a consequence of the presence of unexpected severe ADRs (i.e. 200 points), results in downgrading of a drug from therapeutic innovation to common innovation. These re-assessments of the IAA full final score should be performed under the judgment of the IAA user. In the presence of ADRs that determine the drug's withdrawal from the market, the drug should be considered void of innovative value.

Final considerations

Innovation in the field of pharmacotherapeutics is a burning issue because it can be considered from several different viewpoints, including those of patients, health professionals, healthcare policy-makers, regulatory authorities and/or organizations paying for medicines, and the pharmaceutical industries. The number and relevance of these stakeholders have made it difficult to reach a unanimously agreed definition of drug innovation so far. In a broad outline, Schmid and Smith [11] identified two distinct forms of innovation in the pharmaceutical field: the nonlinear, quantum leap innovation, which is unexpected and unpredictable (e.g. the discovery of penicillin); and the linear, rational innovation, which is typically based on incremental improvements (i.e. the 'incremental value of innovation', applicable, for example, to the antagonist of the histamine type-2 receptor ranitidine with respect to cimetidine).

Although different criteria are available for evaluating innovation in relation to the R&D process of a drug, the most important criterion of drug innovation is therapeutic value (see the ISDB working group's document available at http://66.71.191.169/isdbweb/pag/documents/ISDB-decl-english.pdf). Both the FDA and the EMEA have taken some steps to categorize this value. The American regulatory body categorizes molecules on the basis of their chemical characteristics (e.g. NCEs or incrementally modified drugs) and on their therapeutic potential (i.e. priority drug and standard drug), with the aim of defining the evaluation procedures of registration dossiers and the corresponding deadlines (see the FDA Center for Drug Evaluation and Research Priorities website: http://www.fda.gov/cder/rdmt/pstable.htm; access verified May 2006).

The European regulatory body initially considered that centralized registration procedures should be mandatory for medical products developed by biotechnological processes (recombinant DNA technology, controlled expression of genes coding for biologically active proteins, hybridoma and monoclonal antibody methods) and might also consider the centralized registration of any medicine that demonstrates a relevant therapeutic innovation (Council Regulation No. 2309/93 of 22 July 1993; available at http://pharmacos.eudra.org/F2/eudralex/vol-1/REG_1993_2309/REG_1993_2309_EN.pdf; access verified May 2006). A recent survey suggests, however, that only 47% of all drugs submitted to the EMEA and evaluated with a centralized procedure between 1995 and 2003 represented a real therapeutic innovation [12]. The recent review of European pharmaceutical legislation extended the types of medicine for which the centralized procedure is mandatory. In fact, other than biotechnological products, orphan drugs and NCEs for the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorders and diabetes must be submitted to the EMEA for evaluation with a centralized procedure (Regulation No. 726/2004 of the European Parliament and of the Council of 31 March 2004: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf; access verified May 2006).

In this current situation, the aim of the IAA is to go beyond an initial evaluation of the potential value of innovation of a new drug and to provide an overall assessment of drug innovation, considering, in particular, the relevant properties of innovation from a wider perspective. Furthermore, it is clear that the IAA full final score is dependant on the time span considered and that it is subject to changes over time because the innovative value of any new drug also changes over time.

Several other models have been based on variables that are conceptually similar to those considered by IAA. Some of these simulation tools have been made to evaluate the risks, potential costs and future profits of the development of a new potential medicine out of several compounds in the early stage of the R&D process [13,14]; others analyze similar variables after R&D to address either the price of a new medicine before its introduction onto the market [15] or the level of innovation of a specific compound from the perspective of patients and according to their clinical conditions [16]. Although IAA should be considered as a tool that is specifically useful for regulatory purposes, it runs with information obtained during the early stage of R&D.

In conclusion, the IAA intends to achieve the following goals:

- to provide a score of drug innovation that incorporates the assessment of information generated during both the pre-marketing and the post-marketing authorization phase;

- to provide a flexible assessment, based on a scoring system for a new product, that can be adapted according to both specific features and health objectives of the National Health Service;
- to provide a transparent assessment of drug innovation that could be useful to R&D and regulatory affairs operators and, above all, to health authorities to assess the contribution of an innovative drug to achieving higher standards of public health.

Appendix

The software for the IAA can be downloaded from the website of the Italian Society for Economics and Ethic Studies on Drugs and Therapeutic Treatment [Società Italiana per studi di Economia ed Etica sul farmaco e sugli Interventi Terapeutici (SIFEIT); www.sifeit.it/IAA.html]. The algorithm is supplied with the weightings adopted by the authors. These weightings can be changed by the user on the basis of specific requirements.

Conflicts of interest

The authors have no conflict of interest directly relevant to the content of this contribution. The opinions and conclusions of the authors do not necessarily represent those of the Italian Ministry of Health.

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